REMARKS

Claim 12 has been canceled.

Claim 1 has been amended to recite "contacting a test sample with a peptide substrate specific for a protease that is unique to *Listeria monocytogenes*." Support for this amendment is found in the specification, for example, at page 8, lines 27-29 and Example 1.

Claim 2 has been amended to replace the term "colorimetric" with "chromagenic." Support for this amendment is found in the specification, for example, at page 5, lines 9-16.

Claim 3 has been amended to add detection by a UV lamp. Support for this amendment is found in the specification, for example, at page 16, lines 21-22.

Claim 10 has been amended to recite a "peptide substrate." Support for this amendment is found in the specification, for example, at page 8, line 30 to page 9, line 4 and Table 1.

Claims 17 and 30 have been added. Support for these new claims is found in the specification, for example, at page 5, lines 9-11.

Claims 18 and 31 have been added. Support for these new claims is found in the specification, for example, at page 5, lines 13-14.

Claims 19 and 32 have been added. Support for these new claims is found in the specification, for example, at page .

Claims 20 and 33 have been added. Support for these new claims is found in the specification, for example, at page 5, lines 14-16.

Claims 21 and 34 have been added. Support for these new claims is found in the specification, for example, at page16, lines 21-22 and Claim 3 as originally filed.

Claims 22 and 35 have been added. Support for these new claims is found in the specification, for example, at page 5, lines 21-22.

Claims 23 and 36 have been added. Support for these new claims is found in the specification, for example, in Claim 3 as originally filed.

Claims 24 and 37 have been added. Support for these new claims is found in the specification, for example, at page 8, lines 27-30.

Claims 25 and 38 have been added. Support for these new claims is found in the specification, for example, at page 8, line 30 to page 9, line 4, and Table 1.

Claims 26 and 39 have been added. Support for these new claims is found in the specification, for example, at page 13, lines 4-6.

Claims 27, 28, 40 and 41 have been added. Support for these new claims is found in the specification, for example, at page 6, lines 13-16, and page 17, lines 11-12.

Claim 29 has been added. Support for this new claim is found in the specification, for example, at page 8, line 27 to page 9, line 10 and page 10, line 14 to page 11, line4.

New Claims 17-41 either depend from Claim 1 or, as in the case of Claim 29, are of narrower in scope of Claim 1, therefore, Applicant believes that no additional search is required and that the new claims should be examined with pending Claims 1-3 and 10.

No new matter has been added by the claim amendments or by the new claims. Therefore, entry of this amendment into the present application is respectfully requested.

Claim Rejections 35 U.S.C. § 103

Claims 1-3, 10 and 12 have been rejected under 35 U.S.C. § 103 as being unpatentable over Krafft, G.A. (EP 0428000A1, hereinafter Krafft) in view of Rambach (U.S. 5,716,799, hereinafter Rambach) and further in view of Vollmer *et al., Infection and Immunity, 64*:3646-3651 (1996) (hereinafter, Vollmer). The Examiner believes that it would have been prima facie obvious to one of ordinary skill in the art to combine the methods taught by Krafft, Rambach and Vollmer to obtain the claimed invention. The Examiner believes that Krafft teaches detecting the presence of a pathogenic microorganism, Rambach teaches a method of detecting the presence or absence of Listeria in a sample by using an enzyme substrate chromogen and that Vollmer teaches detection of metalloprotease of *Listeria monocytogenes*, and that the combination of these references makes obvious the claimed invention.

Applicant respectfully disagrees. The rejection relies on an improper combination of references based on impermissible hindsight using Applicant's disclosure as a template to piece together art to support the rejection. Where the claimed invention is rejected as obvious in view of a combination of references, 35 U.S.C. § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* There must also be motivation or suggestion in the prior art to combine elements in the prior art. That is, in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art. *In re Newell* 13 USPQ2d 1248, 1250 (Fed. Cir. 1989). When determining patentability under 35 U.S.C. § 103, the prior art must be considered as a whole,

including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

In order to show why one of skill in the art would not be motivated to combine the cited references, Applicant must clearly summarize the scope and content of the prior art and the differences between the prior art and the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). If one or more of the references cited to support the combination of teachings does not teach what the Examiner believes, then the combination of references fails to support a prima facie case of obviousness. As explained below, Applicant's claimed method of detecting the presence or absence of *Listeria monocytogenes* in a test sample with a peptide substrate specific for a protease that is unique to *Listeria monocytogenes* is not *prima facie* obvious, because the cited references provide neither the requisite suggestion nor a reasonable expectation of success to arrive at the claimed invention.

Claims 1-3 and 10 have been amended. Claim 12 has been canceled. Claim 1, as amended, is directed to a method for detecting the presence or absence of *Listeria monocytogenes* in a test sample comprising the steps of: a) contacting the test sample with a peptide substrate specific for a protease that is unique to *Listeria monocytogenes*; and b) detecting cleavage of the peptide substrate or absence of cleavage of the peptide substrate, wherein cleavage of the peptide substrate is indicative of the presence of *Listeria monocytogenes* in the test sample, and absence of cleavage of the peptide substrate is indicative of the absence of *Listeria monocytogenes* in the test sample. Claim 2, as amended, is directed to the method of Claim 10, wherein the quenched label is selected from the group consisting of fluorescent labels and chromagenic labels. Claim 3, as amended, is directed to the method of Claim 2 wherein the cleavage is detected using a colorimeter, fluorimeter or a UV lamp. Claim 10, as amended, is directed to the method of Claim 1 wherein the peptide substrate is labeled with a quenched label.

Improper Combination of References

None of the Examiner cited references alone or in combination teach or suggest detecting the presence or absence of *Listeria monocytogenes* in a test sample with a peptide substrate specific for a protease unique to *Listeria monocytogenes*.

Krafft teaches a general method of labeling a peptide for detection upon cleavage of the peptide substrate. More specifically, Krafft teaches a fluorogenic substrate made from a fluorescent donor and quenching acceptor attached to a peptide, wherein the peptide can be cleaved by a viral protease enzyme specific for avian myeloblastosis virus or human immunodeficiency virus. (Page 3, lines 16-19). Krafft, however, does not teach detecting the presence or absence of a bacterial pathogen. Therefore, Krafft does not teach or suggest detecting the presence or absence of the bacterial pathogen *Listeria monocytogenes* using a peptide substrate specific for a protease that is unique to *Listeria monocytogenes*, which is the subject matter of Applicant's claimed invention.

Rambach teaches a general method of detecting the presence or absence of enzyme activity in a culture medium. (Col. 1, lines 1-3) The culture medium is characterized in that it requires two components: a chromagen substrate and a carbohydrate. (Col. 2, lines 16-23) Further, Rambach teaches that the culture medium is peptone-based and the organic substrate is specific for particular enzymes (i.e., β-galactosidase, β-glucuronidase). (Col. 2, line 24 and Col. 2, lines 37-41). Rambach mentions Listeria in a list of bacteria whose presence or absence is capable of being demonstrated by the method. (See Col. 3, lines 1-6). Rambach, however, does not teach or suggest a single component peptide substrate. Further, the enzymes taught by Rambach would not cleave the peptide substrate of Applicant's invention. Rambach does not teach a substrate specific for Listeria. Morever, Rambach does not provide any data to demonstrate detecting Listeria.

Vollmer teaches a novel mechanism, distinct from Applicant's method, referred to as shedding, whereby membrane-anchored proteins are released in a functionally active state. (See Page 3546, Col. 1). Further, Vollmer teaches that shedding of interleukin-6 receptor (IL-6R) was detected from cells treated with culture supernatants from organisms such a *L. Monocytogenes*. (See Page 3647, Col. 1). Vollmer, however, does not teach substrate cleavage, which is the subject matter of Applicant's claimed invention.

None of the Examiner cited references alone or in combination teach or suggest detecting the presence or absence of *Listeria monocytogenes* in a test sample with a peptide substrate specific for a protease unique to *Listeria monocytogenes*. As stated above, Rambach teaches a

culture medium that is characterized in that it requires two components: a chromagen substrate and a carbohydrate. Krafft teaches a single component peptide substrate. There is no motivation for one of skill in the art to change the single component peptide substrate of Krafft to a culture medium with two components, as taught by Rambach. There is no motivation for one of skill in the art to change the two component culture medium as taught by Rambach to a single labeled peptide substrate as taught by Krafft. Thus, there is no motivation for one of skill in the art to combine the teachings of Rambach and Krafft.

Further, Vollmer teaches a completely different enzymatic process than Krafft and Rambach. Vollmer teaches the novel process of shedding. Neither Krafft nor Rambach teach or suggest shedding of membrane-anchored proteins. VollmerThere is no motivation for one of skill in the art to combine the novel process of shedding as taught by Vollmer with the process of substrate cleavage as taught by Krafft and Rambach. Thus, there is no motivation to combine the teachings of Vollmer, Rambach and Krafft.

In the Office Action, the Examiner makes a conclusory statement that "one of ordinary skill in the art would have been motivated by the teaching of Krafft that the concept of his invention can be appreciated by one skilled in the art of fluorogenic substrates in other assay procedures (see page 12 Krafft)." However, the Examiner fails to meet the burden of supporting a prima facie case of obviousness. Nowhere does the Examiner explain why one of skill would be motivated to substitute a fluorogenic substrate taught by Krafft with a two component chromagen plus carbohydrate substrate as taught by Rambach. This combination certainly does not make obvious the claimed invention.

Nor does the addition of Vollmer to the combination of Krafft and Rambach cure this deficiency. The teachings of Vollmer are totally irrelevant unless the Examiner can provide evidence of motivation to one of skill in the art toignore the two component chromagen/carbohydrate substrate taught by Rambach and again focus on the use of the peptide substrate taught by Krafft. But even then the Examiner has the burden of providing evidence of the motivation to substitute a membrane bound, unlabeled cytokine receptor (IL-6R) substrate, as taught by Vollmer, for the fluorogenic substrate as taught by Krafft. No combination of these cited references can make obvious the claimed invention.

Impermissible Hindsight

It is clear that the prior art combination of record has been made with the impermissible advantage of hindsight, and thus, the rejection is legally improper. It is axiomatic that when analyzing a reference for its ability to support a prima facie case of obviousness, "[t]he reference must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention." MPEP, 8 th edition, February 2003 revision, § 2141. The content of the prior art reference is determined at the time that the invention was made in order to avoid hindsight reconstruction. MPEP, 8 th edition, February 2003 revision, § 2141.01. The Examiner must forget about what is taught in the application and cast himself back to the date of filing the instant application, to determine the state of the art.

"Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." *In Re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999). "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight." *Id.*

Applicant is the first to describe the claimed method of detecting the presence or absence of *Listeria monocytogenes* in a test sample with a peptide substrate specific for a protease unique to *Listeria monocytogenes*. None of the Examiner cited prior art references alone or in combination teach or suggest the claimed method of detecting the presence or absence of *Listeria monocytogenes* in a test sample, by contacting the test sample with a peptide substrate specific for a protease that is unique to *Listeria monocytogenes*; and detecting cleavage of the peptide substrate or absence of cleavage of the peptide substrate. As discussed above, the Examiner has provided no evidence of motivation to combine the teachings of Krafft with the teachings of Rambach and Vollmer. It is clear that this combination was made as the result of reading Applicant's application and searching the literature for references that provided the "pieces"of the invention blueprint.

Rambach includes Listeria in a list of bacteria that can be detected using a culture medium with two components: a chromagen substrate and a carbohydrate (Col. 3). Rambach

lists microorganisms including yeast, molds and bacteria that are suitable for use in his assay. The mention of Listeria is conceivably the only reason the Examiner chose to cite Rambach in this obviousness rejection. As discussed above, there is no motivation for one of skill in the art to modify the substrate of Krafft to a two component substrate as taught by Rambach for detection of bacteria in culture medium. The assay, performed in culture medium, as taught by Rambach is completely different from the teachings of both Krafft and the teachings of the claimed invention.

Vollmer teaches a novel mechanism referred to as shedding, whereby membrane-anchored proteins are released in a functionally active state. Again, it appears that the only reason that the Examiner chose to cite Vollmer in this obviousness rejection was because Vollmer mentions shedding of IL-6 from metalloproteinase specific for *Listeria Monocytogenes*. Vollmer clearly describes this shedding activity as a novel pathogenic mechanism characteristic of many pathogenic bacteria. Vollmer clearly describes that this shedding activity is found in many bacteria and is not unique to Listeria. The Examiner has relied upon impermissible hindsight to cite these references to support the obviousness rejection.

Obvious to Try

At most, the Examiner's rejection amounts to an assertion that it would have been obvious to try to take the teachings of Krafft to try to make a peptide substrate specific for a protease that is unique to *Listeria monocytogenes*.

The Federal Circuit has long held that "obvious to try" does not constitute obviousness." *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir, 1988). It is not proper for the Examiner to suggest that one of skill in the art "would have var[ied] all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of the many possible choices is likely to be successful...." *Id.* There must be some suggestion or motivation either in the references themselves or in knowledge generally available to one of ordinary skill in the art to try the specific thing claimed.

As stated above, Krafft teaches a general method of labeling a peptide for detection upon cleavage of the peptide substrate. The existence of Krafft's general method for labeling a peptide for detection upon cleavage of the substrate is essentially irrelevant to the question of whether a

method of using substrate cleavage to specifically detect the presence or absence of *Listeria monocytogenes* in a sample would have been obvious, in the absence of other prior art that suggests the claimed method. *See In re Deuel*, 34 USPQ2d 1210, 1215 (1995). There must be prior art that suggests the claimed method. The existence of a general method for labeling a peptide for detection upon cleavage of the substrate, coupled with the idea that *Listeria monocytogenes* could be a suitable target, might have provided motivation to try to modify Krafft's general method of substrate cleavage to detect *Listeria monocytogenes*, does not make obvious the claimed method. However, as stated above, obvious to try does not constitute obviousness. A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out make obvious a particular result. There must be reasonable certainty of success that the method will indeed work. As described above, Rambach, Vollmer and Krafft are an improper combination. There is no reasonable expectation of successfully achieving Applicant's method of detecting the presence or absence of *Listeria monocytogenes* in a test sample with a peptide substrate specific for a protease unique to *Listeria monocytogenes*.

Thus, the Examiner has failed to establish a prima facie case of obviousness based on the combination of teachings of Krafft, Rambach and Vollmer, and Applicant respectfully requests reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Dated: June 8, 2004